

Barrett's Esophagus: Update on Diagnosis and Special Techniques

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History of Barrett's Esophagus

The prominent British surgeon Norman Barrett is generally credited with first describing the condition that bears his name. However, several other astute physicians observed years earlier that patients with esophageal erosions often had adjacent mucosa more closely resembling the glandular mucosa of the stomach than the normal squamous mucosa of the esophagus. In 1950, Barrett published a report describing the anatomic landmarks that define the esophagus; however, he (and others) felt that when the distal portion of this tubular organ was ulcerated and lined by columnar epithelium, it represented a tubular segment of stomach pulled up and tethered within the chest by a congenitally short, squamous-lined esophagus. Subsequently, in the early 1950's, goblet cells were described within the columnar-lined segment. In 1953, Allison and Johnstone argued that this columnar-lined tubular structure was not abnormal stomach but abnormal esophagus, and named the ulcers "Barrett's ulcers." Barrett then published a paper agreeing with their theory in 1957. The first assertion that Barrett's esophagus (BE) was not congenital, but rather a result of reflux esophagitis, was put forth in 1959 by Moersch et al. Interestingly, Barrett himself never mentioned goblet cells as a feature of the columnar-lined esophagus that he described; therefore, it is likely that none of the patients presented in his work actually had Barrett's esophagus as we define it today!

Barrett's Esophagus: Definitions and Terminology

Traditionally, BE has generally been defined as replacement of the normal stratified squamous mucosa of the esophagus by metaplastic columnar epithelium. Currently, however, most authorities (including the American College of Gastroenterologists) agree that the best definition of BE includes both clinical and pathologic conditions:

1. Abnormal glandular mucosa of any length that is recognized in the esophagus at endoscopy
2. Intestinal metaplasia/goblet cells seen at biopsy

Endoscopically, Barrett's mucosa is usually very distinctive: the squamocolumnar junction is displaced proximally, and salmon-pink to red, velvety tongues of glandular mucosa extend upward from the LES region. Involvement by glandular mucosa may be circumferential, or partial and patchy. Islands of squamous mucosa may be visible within the BE field. Erosions may be difficult to distinguish from BE mucosa in some cases. It is important to remember that dysplasia and even intramucosal carcinoma may be present with no mucosal abnormalities other than those consistent with BE. In addition, the diagnosis of BE requires true goblet cells, that is, those that have both the characteristic barrel-shaped morphology and are Alcian blue positive at pH 2.5.

This clinicopathologic definition significantly affects pathology reporting, as illustrated by the scenarios below:

1. The endoscopist sees columnar mucosa, but you don't see goblet cells: no BE
2. The endoscopist sees columnar mucosa, and you see goblet cells: diagnose BE
3. Endoscopist doesn't see columnar mucosa, or is unsure, and you see goblet cells: diagnose goblet cells, with a comment as to the possibilities, and suggest follow up.

The cardia controversy. One of the biggest controversies in the diagnosis of BE involves the distinction between true BE and intestinal metaplasia of the gastric cardia (GCIM). As the diagnosis of BE immediately places the patient in a surveillance program and increases their cancer risk, yet there are no surveillance guidelines for patients with IMGC and the cancer risk is less well defined, the distinction between the two has significant clinical and prognostic importance. The crux of the problem is one of landmarks, and the difficulties inherent in defining the anatomic gastro-esophageal junction. The GEJ is where the tubular esophagus joins the saccular stomach (obviously). However, the mucosal squamocolumnar junction (also known as the z-line, or ora serrata) may not correlate exactly with the location of the GEJ; the squamocolumnar junction is often irregular, and may lie anywhere within the region of the lower esophageal sphincter (LES), that is, within the distal 2-3 cm of the esophagus. The presence of a hiatal hernia may further complicate the identification of these landmarks, plus the fact that the entire area is a dynamically changing structure. Pathologists must rely on an endoscopist to tell them exactly where the biopsies are from. If the endoscopist only reports "GEJ," then there is no way to tell the site of the biopsy. Reporting suggestions are given below, as is a brief discussion of ancillary techniques that have been used to distinguish BE from GCIM.

Pathology

Histology of Barrett's Mucosa

BE is often a mix of fundic, cardiac, and intestinal (goblet) epithelium. In earlier literature, glandular mucosa lacking goblet cells was also considered to be BE. It is important to remember that many of these studies were done blindly without direct visualization of anatomic landmarks, under manometric guidance only. We now know that the presence of goblet cells is required for the diagnosis of BE, as only this type of mucosa confers cancer risk. In addition, both foveolar and fundic type gastric mucosa are normally present in the area of the distal esophagus and GEJ, and do not represent BE.

The typical histologic appearance of Barrett's mucosa is a blend of goblet cells and gastric columnar -type cells. Barrett's mucosa may be flat or villiform. BE typically has the appearance of incomplete intestinal metaplasia, but occasionally complete intestinal metaplasia is seen. Architecturally, nondysplastic BE glands should be rounded in contour, with little budding, and separated by plenty of lamina propria. Nuclei are in general small, uniform, and basally located, with a smooth round nuclear membrane and

small (if any) nucleoli. Focal nuclear stratification is acceptable. Reactive nuclear atypia is acceptable when inflammation is present, as are normal mitoses. Remember that fixation in Hollande's or Bouin's produces more vesicular nuclei with more prominent nucleoli, which may be mistaken for dysplasia.

Proliferating nuclei in the bases of the glands in nondysplastic BE are larger, more hyperchromatic, and more stratified than those at the surface, which generally remain in a monolayer with basally located nuclei. These features should not be misinterpreted as dysplasia.

Other types of metaplasia. Several investigators have reported a multilayered epithelium at the GE junction, similar to that seen in the transformation zone of the uterine cervix, with features of both squamous and columnar mucosa. More recently, a similar multilayered metaplastic epithelium with a ciliated surface has been described. Although some regard these changes as precursor lesions to BE, others regard them as a harmless reactive metaplastic change analogous to pancreatic acinar metaplasia.

Squamous islands. A common finding is the development of macroscopically visible squamous islands within Barrett's epithelium. Some consider this evidence of regression, but the true significance is unclear. This may also represent re-epithelialization at biopsy sites; in addition, this phenomenon has gained increased attention as more patients undergo ablative therapies such as photodynamic therapy. If an area of BE is completely or significantly covered by squamous mucosa, particularly in a patient who has had ablative therapy, it is probably a good idea to note it in the report so that the endoscopist knows to continue to perform surveillance and biopsy on the patient. It is also important to remember that in patients who have undergone ablative therapy, foci of dysplasia and even carcinoma may be buried beneath squamous mucosa.

Special Techniques

Histochemistry

Alcian blue. Alcian blue is perhaps the most widely used special stain in the diagnosis of BE, and many large BE centers perform it routinely. An Alcian blue stain at pH 2.5 stains the acidic mucin (a mixture of sialomucins and sulfated mucins) in goblet cells bright blue, but also stains other non-goblet columnar cells in BE, such as gastric pit and neck cells, gastric surface cells in gastritis and carditis, and sometimes columnar cells in the gastric cardia of patients without BE. Some have designated these non-goblet columnar cells in BE "columnar blues," and have considered them an early marker of intestinal differentiation and thus BE. This remains controversial, however, and most investigators do not regard non-goblet Alcian blue positive columnar cells as diagnostic of BE. Sometimes gastric type foveolar cells become distended (pseudogoblets) and mimic goblet cells. True goblet cells have a barrel shape and stain intensely positive with Alcian blue at pH 2.5. Some prefer a PAS/Alcian blue stain, which will also highlight neutral mucins in addition to the blue staining of acid mucins.

Immunohistochemistry

Cytokeratin Subsets. The use of cytokeratin subsets (specifically, cytokeratin 7 and cytokeratin 20) to distinguish BE from GCIM has engendered a great deal of controversy. Some studies have shown that BE has a unique pattern of reactivity when these cytokeratins are applied, specifically, that there is superficial band-like CK20 staining, and strong CK7 staining in both superficial and deep glands. Conversely, gastric intestinal metaplasia showed different patterns of immunoreactivity, depending on the presence of either complete or incomplete intestinal metaplasia. However, other investigators have not been able to duplicate results of the initial CK7/20 studies. Possible explanations for this include different methods, fixatives, and reagents; different definitions of BE and thus sampling bias; and differences in interpreting immunostains. Regardless of the explanation, the lack of reproducibility has led to reservations regarding the clinical utility of cytokeratin subsets. If there is a question as to biopsy location, and thus exact location of the intestinal metaplasia, clarification of the site with the gastroenterologist may be helpful. If not, mapping the stomach and esophagus to ascertain the location and/or extent of intestinal metaplasia should clarify the issue.

Cdx2. The Cdx2 gene encodes an intestine-specific transcription factor that has been reported to regulate both proliferation and differentiation of intestinal epithelial cells. Cdx2 is expressed by normal intestinal and pancreatic cells, and by gastric and esophageal intestinal metaplasia. Normal esophageal and gastric epithelial cells are negative. It has also been shown that both goblet cells and nongoblet columnar cells in BE are Cdx2 positive, and in a minority of cases patients with only nongoblet columnar cells, and no goblet cells, show Cdx2 reactivity. Some authors have argued that this represents early intestinal phenotypic development prior to the development of easily observable goblet cells (analogous to the controversy over “columnar blues”), but this is unproven and most do not recommend it for clinical use at this time.

Mucin Immunohistochemistry The four major secretory mucins seen in intestinal metaplasia are MUC2, MUC5AC, MUC5B, and MUC6. MUC1, MUC3, and MUC4 are membrane bound mucins that have also been demonstrated in BE. Although extensive research has been done to define the mucin profiles of BE, and to attempt to associate certain mucins with the potential for dysplasia and carcinoma, these are not currently used for routine diagnosis.

Other Adjunctive Diagnostic/Screening Techniques

The most common adjunctive technique is flow cytometry. There are data suggesting that an early preneoplastic change in many patients is the development of cells with large changes in DNA content. However, this test is only available at select centers that follow large populations of Barrett's patients. There are many genetic abnormalities thought to be involved in the progression of BE to dysplasia and carcinoma as well, but so far none are routinely used for prospective screening or prognostication.

Communication with Gastroenterologist

This is perhaps the cheapest and easiest adjunctive technique for the diagnosis of BE. Effective communication between endoscopist and pathologist is of paramount importance when dealing with BE. The endoscopist should indicate the exact site of the biopsy, e.g. "esophagus at 30 cm," or "gastric cardia." A description is also critical regarding the endoscopic presence or absence of mucosa consistent with Barrett's. Many authorities recommend the following approach to biopsy in a patient with BE, although everyone recognizes that these are guidelines for an ideal world and that most practitioners will not necessarily take the time or expense to follow such a protocol (or communicate effectively with their pathologist):

1. One bx from proximal stomach, 2 cm below LES, to evaluate gastric cardia and make sure distal part of Barrett's is sampled
2. One bx at the LES
3. 2-4 bx every 2 cm of the length of the Barrett's segment, one from each wall or each quadrant
4. One bx from squamous epithelium proximal to BE
5. Bx of any masses, ulcers, strictures, or other lesions

Pitfalls

BE should not be confused with inlet patches, or ectopic gastric mucosa, in the upper cervical esophagus. Normal esophageal mucous glands, lying within the lamina propria and communicating with the esophageal lumen, should also not be mistaken for BE.

Pancreatic acinar metaplasia should not be confused with BE, as sometimes happens when the metaplastic acinar-like cells are mistaken for Paneth cells.

The most common pitfall in reporting BE is failing to require the two criteria listed above, i.e. both endoscopically visible columnar esophagus and goblet cells on biopsy. This most commonly happens in the following scenarios:

1. An endoscopist biopsies a normal esophagus in a symptomatic patient, and a few goblet cells pop up. In this circumstance, describe the findings, but state that in the absence of visible columnar lined esophagus the significance is unclear.
2. The requisition only says "GEJ," and you don't know what side of the GEJ the biopsy is from. In this circumstance, describe findings, but state that you can't tell if it's BE or GCIM, and that correlation with exact site, or possibly re-evaluation with biopsies of both areas clearly designated, is recommended.

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